Online measurement of oxygen enables continuous noninvasive evaluation of human-induced pluripotent stem cell (hiPSC) culture in a perfused 3D hollow-fiber bioreactor.

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Public Summary:
This paper describes the importance of real-time measuring oxygen consumption during cell culture in a specific 3D bioreactor.

Scientific Abstract:
For clinical and/or pharmaceutical use of human-induced pluripotent stem cells (hiPSCs), large cell quantities of high quality are demanded. Therefore, we combined the expansion of hiPSCs in closed, perfusion-based 3D bioreactors with noninvasive online monitoring of oxygen as culture control mechanism. Bioreactors with a cell compartment volume of 3 or 17 ml were inoculated with either 10 x 10(6) or 50 x 10(6) cells, and cells were expanded over 15 days with online oxygen and offline glucose and lactate measurements being performed. The CellTiter-Blue(R) Assay was performed at the end of the bioreactor experiments for indirect cell quantification. Model simulations enabled an estimation of cell numbers based on kinetic equations and experimental data during the 15-day bioreactor cultures. Calculated oxygen uptake rates (OUR), glucose consumption rates (GCR), and lactate production rates (LPR) revealed a highly significant correlation ($p < 0.0001$). Oxygen consumption, which was measured at the beginning and the end of the experiment, showed a strong culture growth in line with the OUR and GCR data. Furthermore, the yield coefficient of lactate from glucose and the OUR to GCR ratio revealed a shift from nonoxidative to oxidative metabolism. The presented results indicate that oxygen is equally as applicable as parameter for hiPSC expansion as glucose while providing an accurate real-time impression of hiPSC culture development. Additionally, oxygen measurements inform about the metabolic state of the cells. Thus, the use of oxygen online monitoring for culture control facilitates the translation of hiPSC use to the clinical setting.